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Clinical paper

Clinical evaluation of intravenous alone versus intravenous or intraosseous access for treatment of out-of-hospital cardiac arrest

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Abstract

Objective: Obtaining vascular access during out-of-hospital cardiac arrest (OHCA) is challenging. The aim of this study was to determine if using intraosseous (IO) access when intravenous (IV) access fails improves outcomes.

Methods: This was a prospective, parallel-group, cluster-randomised study that compared 'IV only' against 'IV + IO' in OHCA patients, where if 2 IV attempts failed or took more than 90 s, paramedics had 2 further attempts of IO. Primary outcome was any return of spontaneous circulation (ROSC). Secondary outcomes were insertion success rate, adrenaline administration, time to adrenaline and survival outcome.

Results: A total of 1007 patients were included in the analysis. An Intention To Treat analysis showed a significant difference in success rates of obtaining vascular access in the IV + IO arm compared to the IV arm (76.6% vs 61.1% p = 0.001). There were significantly more patients in the IV + IO arm than the IV arm being administered prehospital adrenaline (71.3% vs 55.4% p = 0.001). The IV + IO arm also received adrenaline faster compared to the IV arm in terms of median time from emergency call to adrenaline (23 min vs 25 min p = 0.001). There was no significant difference in ROSC (adjusted OR 0.99 95%CI: 0.75−1.29), survival to discharge or survival with CPC 2 or better in both groups. A Per Protocol analysis also showed there was higher success in obtaining vascular access in the IV + IO arm, but ROSC and survival outcomes were not statistically different.

Conclusion: Using IO when IV failed led to a higher rate of vascular access, prehospital adrenaline administration and faster adrenaline administration. However, it was not associated with higher ROSC, survival to discharge, or good neurological outcome.

Keywords: Resuscitation, Out-of-hospital cardiac arrest, Prehospital, EMS, Intraosseous, Intravenous, Adrenaline

Introduction

Background

Out of hospital cardiac arrest (OHCA) is a global problem with generally poor outcomes. In Singapore, historically the rate of prehospital return of spontaneous circulation (ROSC) was 10%, emergency department ROSC 30.9%, with survival to discharge at 3.2% (all events) and 11.0% for witnessed, shockable rhythms.[1] The national ambulance service — Singapore Civil Defence Force (SCDF) protocol for OHCA includes the use of mechanical CPR (LUCAS), defibrillation, laryngeal mask airway, vascular access and intravenous adrenaline.

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Obtaining vascular access in OHCA cases are challenging due to a variety of reasons. They can be classified into the following:

1 Patient factors: Patients with challenging habitus e.g. the morbid obese and elderly patients with frail skins. It is also challenging to cannulate cardiac arrest patients due to collapsed veins.
2 Environmental factors: Patients may be found in challenging circumstances eg in tight spaces or lying on the floor. Some cannulations also occur in a moving ambulance and this has its own difficulties.
3 Paramedic training and protocols: Basic Life Support (BLS) trained paramedics also have fewer indication for intravenous medications compared to Advanced Life Support (ALS) trained paramedics.

Importance

Intraosseous (IO) access is a viable alternative to intravenous access (IV). Based on European Resuscitation Council guidelines for advanced life support (ALS), the main indication for IO in adult and paediatric patients[2] is emergent vascular access when IV access is "difficult or impossible" in both the prehospital and hospital setting. IO can be inserted manually or using an automated device. Examples of commercially available devices include EZ-IO, bone injection gun (BIG) and FAST1.

Possible IO insertion sites include the proximal tibia, proximal humerus, distal tibia and sternum. The humeral site is associated with more unsuccessful attempts,[3,4] possibly because of difficulty in locating landmarks,[5] while the sternal site interferes with cardiopulmonary resuscitation. In prehospital OHCA, EZ-IO has been used as second line therapy when IV failed, although these studies had small sample sizes. Between 58−95 patients received tibial IO for each study with success rates between 89.7% to 97%.[3,6–8] Studies on automated devices have found a higher success rate for EZ-IO compared to BIG[9] or FAST1.[10]

Previous pilot studies with small sample sizes, on the feasibility of IO in Singapore showed a high success rate with the EZIO,[11] and especially with the tibial insertion site. Good flow was also achieved with the tibial site, although the highest flow rate was with humeral insertion,[12] with the poorest with the distal tibia.[13] Flow rate improved when a pressure bag was applied. Hence, we decided to use the EZIO as our IO device as it was also more widely used in Singapore. The landmark for IO insertion chosen was the proximal tibia in view of the easy identification of landmarks and minimal interference with resuscitation efforts/cardio-pulmonary resuscitation.

Goals of this investigation

In this study, we aimed to determine if the use of IO after 2 failed IV attempts improved outcome of OHCA patients managed by SCDF paramedics in Singapore. Our primary outcome was any ROSC. The secondary outcomes were insertion success rate, proportion of patients receiving the 1st dose of adrenaline on scene, time to adrenaline administration, survival to 30 days post arrest or discharged alive, and survival with good neurological outcome.

Methods

Study design and setting

This was a prospective, parallel-group, cluster-randomised study comparing 'IV + IO' and 'IV only' protocols in patients with OHCA who were managed by SCDF. The EZ- IO was chosen by the SCDF for IO insertion. The proximal tibia was the preferred site for IO attempts due to easy identification of the anatomical landmark and minimal interference of CPR efforts. The trial aimed to recruit all eligible OHCA patients attended to by SCDF over 2-year period. The 1st phase consisted of a run-in phase from August 2014, followed by data collection from September 2014 to October 2015. The 2nd phase started on November 2015−December 2016 (Appendix 1).

Minimum sample size required was calculated based on the main end-point of ROSC. ROSC rates in Singapore were 10% (IV only protocol) based on Lai et al.,[1] compared with 25% reported in advanced life support emergency medical services (ALS EMS) systems. Based on a difference of 15% in ROSC rates between the 2 arms (10% for IV, 25% for IV + IO based on the ALS EMS rate), with 90% power and α of 0.05, the minimum sample size per group was 504 patients. Allowing for loss to follow up and non-compliance to protocol, the trial needed to recruit a minimum of 1200 eligible patients for both phases.

Interventions

30 SCDF ambulances in 16 fire stations provided 'IV + IO' and 'IV only' treatments in 2 consecutive phases. The order of treatment was randomised using stratified randomisation as each fire station had a varying number of ambulances which may be a confounding factor. The 1st, 2nd, 3rd and 4th stratum consisted of fire stations equipped with 1, 2, 3 and 4 ambulances respectively. A block randomisation method was used to take into account the small probability that stations with more ambulances might have more experienced paramedics (higher volume) than those with fewer ambulances. Block randomisation was done for each stratum to randomise which fire stations would administer 'IV + IO' or 'IV only' in the 1st phase, and then the other treatment in the 2nd phase as per the crossover design (Appendix 1). Paramedics completed the manufacturer's training programme and were familiar with the protocol before they could use the device. The public affairs department from SCDF informed the new treatment method to the public via local mainstream media such as newspapers and national news broadcasting television. The Centralised Institutional Review Board approved the ethics application for this study. This study was registered in ClinicalTrials.gov Identifier: NCT02088736.

The treatment protocol for the 'IV only' arm: peripheral IV would be attempted up to twice at scene, up to 90 s for each attempt. If unsuccessful, further attempts could be made in the ambulance. The treatment protocol for the 'IV + IO' arm was: if peripheral IV was unsuccessful after 2 attempts or 90 s, an IO attempt was allowed at the primary site (proximal tibial). If the IO attempt was unsuccessful at the scene, a 2nd IO attempt could be made in the ambulance during transport (Fig. 1). There was no other 'rescue therapy' in our service. If crews were unable to obtain IV/IO access in the field, they were required to 'scoop and run', with further attempts allowed in the ambulance en-route.

Inclusion criteria were: patients with cardiac arrest (medical) requiring intravenous fluids or medications. The IO inclusion criteria was: adult OHCA, resuscitation attempted by EMS. Exclusion criteria included paediatric patients (age $\leq$ 14 years) and trauma cases. The IO exclusion criteria included obvious or suspected tibia or femur fracture, recent surgery in the last 2 weeks in the extremity to be used or previous orthopaedic procedures such as total knee replacement, correction of the tibia or femur, above or below the knee amputation, pre-existing medical conditions such as peripheral vascular disease,

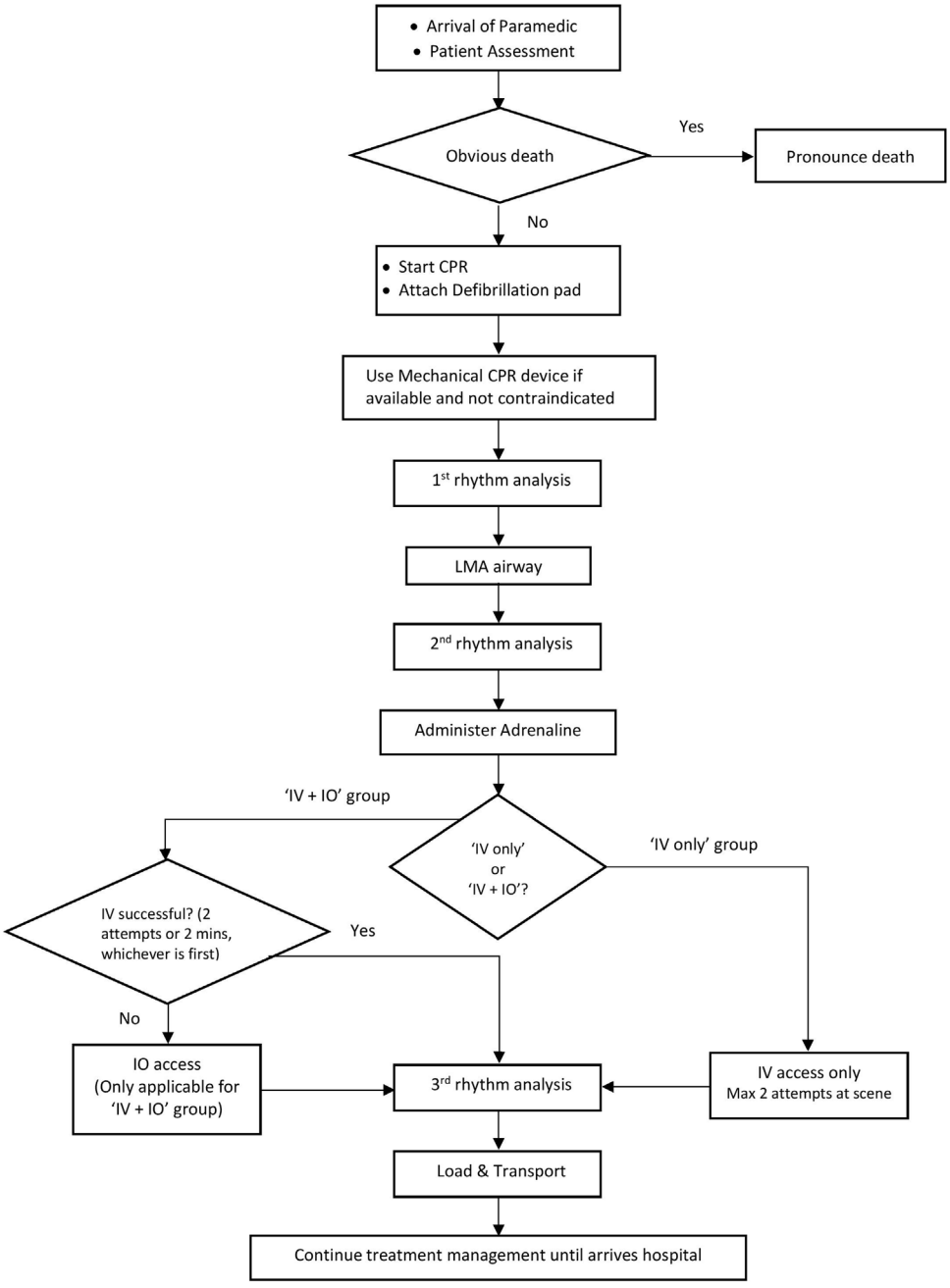

Fig. 1 – Cardiac arrest for adult protocol.

tumour in the lower limb, infection including cellulitis at the insertion site, and inability to locate landmarks due to lower limb oedema or obesity. The contralateral tibia might be considered for insertion if it did not have any contraindications (Appendix 2).

Outcomes

Primary outcome was any ROSC, which was the endpoint of this trial. In our service, any ROSC was defined as return of electrical activity confirmed by a palpable pulse for at least 5 min during pre or in-hospital periods after either IV or IV + IO access was attempted. Secondary outcomes included insertion success rate, proportion of patients who received the1st dose of adrenaline, time taken for the 1st dose of adrenaline which was defined as time between arrival at the patient's side and the 1st dose of adrenaline administered, survival outcome as defined by survival in hospital at day 30 post arrest, or discharged alive. The neurological and functional outcome was defined by cerebral performance category (CPC) and overall performance category (OPC) respectively, where a score of 1 or 2 was a good outcome. Immediate adverse effects of IO or IV insertion were recorded.

Measurements

Study forms were matched against the Singapore OHCA database which was part of the Pan-Asian Resuscitation Outcomes Study

(PAROS), to complement data collection and to determine hospital outcomes as the study forms collected only prehospital information.

Analysis

Statistical analysis included t-test, Mann–Whitney *U* test, chi-square test, with odds ratios from multivariate logistic regression which was used to adjust for relevant covariates (gender, age, arrest unwitnessed, bystander CPR, bystander AED, prehospital defibrillation and first arrest rhythm) in the analysis of the primary endpoint of ROSC. Analysis was conducted on an Intention to Treat (ITT) basis as we included the possibility that IO insertion may not have been performed in the IV and IO arm for various reasons. We also performed a per protocol analysis, which included all patients who completed the study without major protocol deviations and remained in their original assigned treatment group.

Results

Characteristics of study subjects

Fig. 2 shows a CONSORT flowchart of the trial. There were a total of 1103 cardiac arrests that the SCDF responded to, 845 in Phase 1 and 258 in Phase 2, out of which 87 cases were excluded. 33 were traumatic and paediatric cases and 3 others were excluded due to unknown reasons. Thus, a total of 1016 patients were enrolled into the study. After block randomisation, the IV arm had 481 patients. 3 were lost to follow up and a total of 478 patients were analysed. The IV and IO arm had 535 patients. 6 were lost to follow up and a total of 529 patients were analysed.

Baseline characteristics from both groups did not show any significant difference and they are shown in Table 1. However, it should be noted that both groups had a large number of patients that

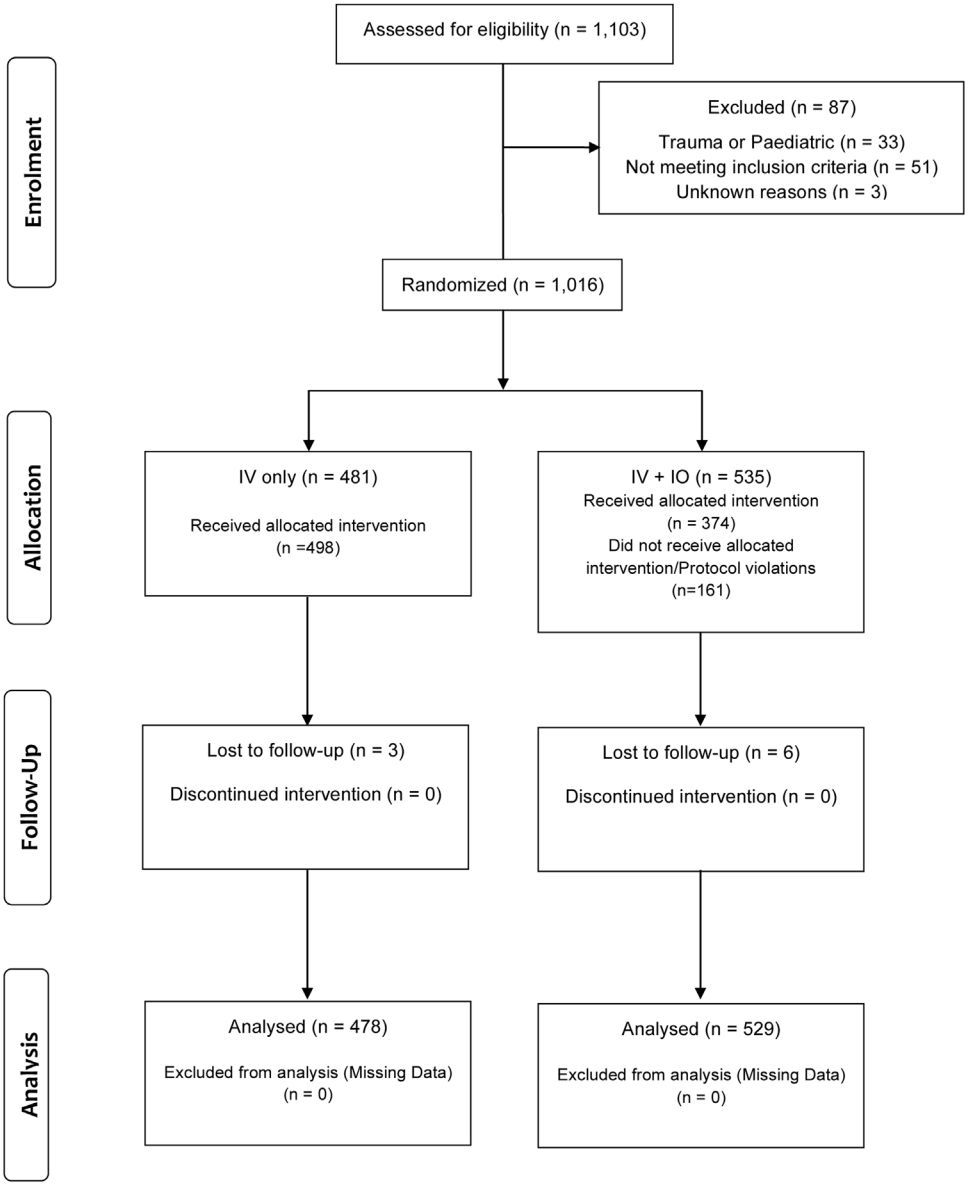

Fig. 2 – CONSORT flow chart of the trial (Intention to Treat analysis).

Table 1 – Characteristics of study patients.

Baseline characteristics	IV only (n = 478)	IV + IO (n = 529)	p Value
Median age (years) (IQR)	67 (54–78)	68 (55–80)	0.126
Gender (male)	313 (65.5%)	342 (64.8%)	0.814
Race			
Chinese	305 (63.8%)	360 (68.1%)	0.365
Malay	77 (16.1%)	75 (14.2%)	
Indian	70 (14.7%)	62 (11.7%)	
Others	26 (5.5%)	32 (6.0%)	
Arrest witnessed	286 (60.2%)	325 (61.7%)	0.636
By paramedics	49 (17.1%)	47 (14.5%)	0.365
Bystander CPR present	229 (48.6%)	244 (46.7%)	0.810
Bystander AED present	10 (2.1%)	14 (2.7%)	0.573
First arrest rhythm			
VT/VF	99 (21.0%)	82 (15.8%)	0.034
PEA	126 (26.7%)	178 (34.3%)	
Asystole	228 (48.3%)	237 (45.7%)	
Unknown	19 (4.0%)	22 (4.2%)	
Prehospital defibrillation	144 (30.6%)	157 (30.0%)	0.834

Access outcome (secondary aims)	IV only (n = 478)	IV + IO (n = 529)	p Value
Total vascular access successful	292 (61.1%)	405 (76.6%)	0.001
Total prehospital adrenaline administered	265 (55.4%)	377 (71.3%)	0.001
Median time from emergency call to adrenaline (minutes) (IQR)	25 (20–31)	23 (18–28)	0.001
Median time from arrival at patient's side to adrenaline (minutes) (IQR)	11 (7–18)	9 (6–14)	0.001
1st/2nd attempt IV successful (as per protocol)			
1st attempt successful	131 (27.5%)	144 (27.2%)	0.846
2nd attempt successful	90 (18.9%)	93 (17.6%)	
Not successful	257 (53.8%)	292 (55.2%)	
IO attempted (as per protocol)			
1st attempt IO successful	NA	127 (43.5%)	NA
2nd attempt IO successful		4 (1.4%)	
IO failed (1st attempt failed, no 2nd attempt)		36 (12.3%)	
No attempt		125 (43.2%)	
Median number of IV attempts (IQR)	2 (1–3)	1 (0–2)	0.001
Survival outcomes	IV only (n = 478)	IV + IO (n = 529)	p Value
Any ROSC	178 (37.2%)	196 (37.1%)	0.951
Prehospital ROSC (Primary aim)	56 (11.7%)	62 (11.7%)	0.998
Hospital ROSC	132 (27.6%)	143 (27%)	0.836
Died in the emergency department or in hospital	435 (91%)	499 (94.3%)	0.042
Survive to discharge or 30 days	40 (8.4%)	26 (4.9%)	0.027
Total with CPC, OPC $\leq$ 2	19 (4%)	18 (3.4%)	0.630

IQR: inter-quarter range; CPR: AED: automated external defibrillator; VT: ventricular tachycardia; VF: ventricular fibrillation; PEA: pulseless electrical activity; ROSC: return of spontaneous circulation; CPC: cerebral performance category; OPC: overall performance category.

presented with a non-shockable initial rhythm. There were no significant differences between both groups.

Main results

Results on the IV and IV + IO vascular access groups are reflected in Table 1. There was a significant difference in success rates of obtaining vascular access in the IV + IO arm compared to the IV arm (76.6% vs 61.1% p = 0.001). Both groups had similar IV success rates for 1st and 2nd attempts. When IO was indicated in the IV + IO arm (n = 292), 43.5% were successful on the 1st attempt, 1.4% were successful on the 2nd attempt. There was a 12.3% failure rate where there was only 1 IO attempt and no 2nd attempt was carried out. 43.2% (n = 125) had no IO attempted at all. Various reasons (Table 2) given for no IO attempted when indicated ranged from no available stock to insufficient time. There were around 72 out of the 125 cases where IV was attempted more than twice.

There were significantly more patients in the IV + IO arm than the IV arm being administered prehospital adrenaline (71.3% vs 55.4% p = 0.001). The IV + IO arm also received adrenaline faster compared to the IV arm in terms of median time from emergency call to adrenaline (23 min vs 25 min p = 0.001). Conversely, the IV + IO arm patients had a better median time from arrival at patient's side to those in the IV arm.

Table 2 – Reasons why IO was not administered when indicated in the IV + IO group.

	IO indicated after 2 failed IV attempts (n = 125)
No stock	6
Insufficient time/reached hospital	7
Contraindicated	4
No reason given	22
Unable to obtain a clear medical history	4
More than 2 IV attempts	72
Other	10

Table 3 – Logistic regression for primary outcome of ROSC with odds ratio.

Study arm ('IV only' as reference variable)	Prehospital ROSC		Hospital ROSC		Total ROSC	
	Odds ratio [95% CI]	p Value	Odds ratio [95% CI]	p Value	Odds ratio [95% CI]	p Value
Unadjusted for other confounders	0.99 (0.67–1.45)	0.953	0.96 (0.72–1.27)	0.774	0.98 (0.76–1.27)	0.881
Adjusted for gender, age, arrest unwitnessed, bystander CPR, bystander AED, prehospital defibrillation and first arrest rhythm	0.97 (0.64–1.46)	0.868	0.97 (0.72–1.31)	0.828	0.99 (0.75–1.29)	0.918

There was no significant difference in ROSC reported in the IV + IO arm compared to the IV arm (adjusted OR 0.99 95%CI: 0.75–1.29) (Table 3). This included both in the prehospital and hospital environment (Table 1). There was no significant difference in survival to discharge or within 30 days or survivability with CPC 2 or better in both groups as well (IV only 3.4% vs IV + IO 4.0%, p-value 0.630), although there was a hospital death difference (IV only 91.0% vs IV + IO 94.3%, p = 0.042) and survival to discharge/30 days (IV only 8.4% vs IV + IO 4.9%, p = 0.027). The most common immediate complication reported for IO was no or low flow (n = 15). With another 7 reporting other reasons which was not stated (Table 4).

A post hoc "Per Protocol analysis" was performed given the unexpectedly large number of patients who were randomised to IV + IO but did not receive their assigned means of vascular access. In the Per Protocol analysis (see figure in Appendix 3), a total of 161 (125 IO cases with no attempt at all, 36 IO cases with 1st attempt IO failed and subsequently no 2nd attempt) were excluded from the 'IV + IO' arm analysis. 6 cases were lost to follow-up. Hence 368 cases in the 'IV + IO' arm while 478 cases in the 'IV only' were eventually analysed (see table in Appendix 4). There were significantly higher success rates for obtaining total vascular access in the IV + IO arm compared to the IV arm (100% vs 61.1% $p < 0.001$) and successful prehospital adrenaline administered (93.5% vs 55.4% $p < 0.001$). However there was no significant difference in ROSC reported for both arms (IV + IO 38.6% vs IV only 37.2% p = 0.721. The survival outcomes were also not significantly different (survived to discharge IV + IO 4.9% vs IV only 8.4% p = 0.054, Survived with good CPC IV + IO 3.3% vs IV only 4.0% p = 0.713).

Discussion

In this study we found that IO in addition to IV leads to a better vascular access rate and prehospital adrenaline administration. However, delayed IO did not improve clinical outcomes, such as ROSC, survival to discharge or 30 days, or good neurological outcome. In fact, there was a trend towards poorer outcomes in the IV + IO group. Our results showed that the median time from the time the emergency call was made to adrenaline administration was more than 20 min in both 'IV only' and 'IV + IO' groups, although the time taken was significantly shorter in the 'IV + IO' group. However, it is noted that the median time for adrenaline administration from time of arrival at patient's side was much shorter, 9 min for IV + IO group and 11 min for the IV only group. Thus it was surprising that we were unable to see a significant difference in ROSC rates in both arms, even in the 'Per Protocol analysis' (see Appendix 4).

Previous studies demonstrated a better neurological outcome if the time between the start of CPR and adrenaline administration was within 10 min,[14,15] while another study only found such a benefit in patients with an initial rhythm of VF if the time from the emergency call to adrenaline administration was within 10 min.[16] Another study showed that if adrenaline was administered within 10 min from time of the emergency call to adrenaline administration compared to more than 10 min, this improved ROSC but not long-term outcomes.[17,18] In fact, there is some suggestion from our data that adding IV + IO showed poorer survival, perhaps related to prolonged scene time and evacuation. Hence, future strategies may include attempting IO on first attempt instead of an IV + IO strategy, paired with high performance CPR. However, a cost benefit analysis is needed to assess for long term sustainability of such an approach as the emergency ambulance service is free in Singapore and the cost of IO is absorbed by the ambulance service.

Another possible reason that may contribute to our study's results was that there was actually a relatively small number of IOs that were actually inserted in the 'IV + IO' group. Despite our data being analysed as per Intention to Treat protocol, this could affect data in relation to drug administration times as well as survival rates. This could be due to paramedics being uncomfortable or unfamiliar with IO. Some paramedics have also reported that family members did not want the procedure performed. This may be due to unfamiliarity and lack of awareness of IO by the public and was despite information about the IO trial being published in the local newspaper and local television news. It is thus possible that refinement of IO protocols to using IO as first line for cardiac arrest cases and better public awareness may show more promising results in terms of drug timings and ROSC.

Our study results show that the most common cause of IO failure was no flow or low flow. Other studies have reported other types of IO complications, including extravasation which can lead to compartment syndrome[19,20] and osteomyelitis,[5] which was reported as 0.6% in a review.[21] Most other complications were case reports. These included skin necrosis requiring amputations,[22,23] tibial fractures[24–26] and abscesses.[27] Air embolism has been detected in cases where post-mortem computed tomography was done, however the causes of

Table 4 – IV and IO complications (by treatment received).

Complication	IV only (n = 478)	IV + IO (n = 529)
Catheter displacement	15	NA
No flow	33	
Low flow	6	
Needle breakage	0	
IO only		
No or low flow		15
Others		7

death were uncertain.[28,29] As far as we were aware, we did not see such complications in our study. However, our study forms only collected information about immediate complications.

There were several limitations in the study. One large limitation of the study was protocol violations to the trial protocol. 36 cases had failed IO insertions during 1st attempt and subsequently no 2nd attempt and 125 cases did not receive IO despite being indicated for various reasons. This non-compliance might be reflecting a series of problems with staff training, study protocols, issues with equipment etc. Another limitation of the study was that only immediate complications were documented. As this was a multicentre study, it was logistically difficult to follow up on longer-term complications. We also did not have in-hospital treatment data between groups. We also advise caution when interpreting the per-protocol analysis as it was post-hoc and subject to bias. It only included patients in the IV + IO arm who were not excluded by provider bias, but the value in this case is in providing additional insights into the findings of the ITT analysis.

Another possible limitation is that despite calculating the sample size to include dropouts and such, it may not have taken into consideration the small number of actual IOs done. Another limitation which was unfortunately not within our control was the time to recognition of a cardiac arrest. This is despite intensive work with our telephone despatchers to help people identify OHCA over the phone, deliver telephone instructed CPR, and public outreach programs. This limitation can potentially affect our primary outcome and it could be worth repeating a similar study when data shows that time from emergency call to adrenaline improves. Finally, IO was only used as a 'rescue therapy' in this real-world implementation study and this delay has to be factored in any interpretation of the results.

Conclusion

Using IO after failed IV attempts led to higher vascular success rate, a higher percentage of prehospital adrenaline administration and faster adrenaline administration. However, it was not associated with higher ROSC, survival to discharge, or good neurological outcome. An EMS strategy of IV + IO may not lead to improved OHCA outcomes.

Conflicts of interest

All authors did not have any conflict of interest, commercial, financial, and other relationships as related to this study. The study was awarded by National Medical Research Council (NMRC) Clinician Scientist Individual Research Grant in Singapore (CNIG13may012).

CRediT authorship contribution statement

Boon Kiat Kenneth Tan: Conceptualization, Methodology, Funding acquisition. **Yun Xin Chin:** Writing - original draft, Validation, Visualization. **Zhi Xiong Koh:** Project administration, Resources, Validation. **Nur Ain Zafirah Bte Md Said:** Resources, Investigation. **Masnita Rahmat:** Resources, Investigation. **Stephanie Fook-Chong:** Formal analysis. **Yih Yng Ng:** Supervision, Methodology. **Marcus Eng Hock Ong:** Supervision, Methodology.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2020.11.019.

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